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Process for the purification of losartan

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REPUBLIC OF SLOVENIA
MINISTRY OF SCIENCE AND TECHNOLOGY

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REQUEST FOR A PATENT GRANT

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Acknowledgement of the application
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5. Title of invention:

Process for the purification of losartan

6. Claimed priority right:

7. Additional requests:
- ☐ application for a shortened duration patent
- ☐ preliminary publication after the expiry of ___months
- ☐ application is divided from the application no.:___

8. Statements:
- ☐ statement of common representative

9. Enclosures:

- x Description of the invention, having 25 pages
- x Patent claim (claims), having 3 pages; number of claims: 24
- x Schemes (if required for patent description); number of sheets: 14
- x Abstract
- ☐ Voucher for the settlement of fees
- ☐ Declaration of depositing the biological material if it is an invention which cannot be described
- ☐ Authorisation to the representative
- ☐ General authorisation to the representative is deposited in the office under no. .....
- ☐ Declaration on priority right
- ☐ Information about additional applicants
- ☐ Information about additional inventors
- ☐ Presentation of nucleotide or amino acid sequence in the description
- ☐ Application was previously faxed or mailed in electronic form
- x _____ Information about additional inventors _____

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Annex to the request for a patent grant

Information about additional inventors:

Process for the purification of losartan

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Process for the purification of losartan

Field of the invention
(IPC[7] B01D, A61K)

The present invention belongs to the field of chemistry of heterocyclic compounds and of pharmaceutical industry and relates to a new mode of the purification of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole known under the generic name losartan and the preparation of alkali and alkali-earth salts of losartan useful in the new process of purification.

Technical problem

2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole acts on the last step of the cascade renin-angiotensin system by binding to the angiotensin II receptor. By utilizing said biochemical effect losartan is generally used as an effective antihypertensive agent in the form of the potassium salt (referred to as losartan potassium).

There is a need for losartan and losartan potassium, respectively, of high purity and for a novel process according to which it would purified in a simply performable and rugged way and with a high yield and high purity. It is also desirable to have the active substance in such a form to be simply incorporated into a pharmaceutical formulation which affords high bioavailability. To be incorporated into a pharmaceutical formulation the active substances must have defined desired physicochemical properties.

Prior art

The substituted imidazoles with the action on the renin-angiotensin system of the blood pressure regulation including losartan are disclosed in the patent EP 253310 and US Pat. No. 5,138,069.

The applicants of the patent EP 253310 have protected in general different substituted imidazoles and the salts thereof, including ammonium, calcium, potassium and sodium salts and, specifically have described the reactions leading to potassium and sodium salts of certain substituted imidazoles and have characterized the products thereof. Surprisingly, the compound 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole, later named losartan, in the experimental part it was described only in a non-salt form, that is, in an amphoteric form. The experimental part of that patent discloses that in the synthesis of losartan from cyanobiphenyl intermediate (that is, from 2-*n*-butyl-4-chloro-1-[(2'-cyanobiphenyl-4yl)-methyl]-5-(hydroxymethyl) imidazole) with sodium azide losartan is produced in a form of slightly yellow crystals. The patent also compares the efficacy of a sodium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl] methyl]-1H-imidazole in lowering blood pressure before and after furosemide administration to the animals, however, the compound in the patent or any other application is neither characterized not entered in the register of Chemical Abstract.

Chemical Abstracts Register, among the compounds with losartan structural formula or salts thereof, describes losartan in its basic, that is, amphoteric form; compounds with tetrahydrofuran and with pyridine; a mixture with hydrochlorothiazide, acid addition complexes hydrochloride and hydrobromide, and of the salts *p*-toluenesulfonate and a potassium salt, and hydrochloride of a potassium salt. This suggests that other alkali and alkali-earth salts of losartan have not been characterized and hence their useful properties are unknown.

For incorporation into a pharmaceutical formulation, pharmaceutical active substances must have defined desired physicochemical properties such as: solubility in water and certain solvents, suitable particle size, stability, nonhygroscopicity; which can be regulated by selecting an appropriate salt, adduct complex and form, thereby achieving effective bioavailability.

Alkali or alkali-earth salts of losartan can be prepared because of the acid hydrogen atom on the tetrazole ring which may be split with a sufficiently strong base, that is, with such base which provides the pH of an aqueous solution at the equivalent point which, according to US Pat. No. 5310928, is about pH = 10. EP 324377 describes the process for the formation of a potassium salt of losartan with potassium hydroxide; thereafter a potassium salt has been adopted as the most convenient form of the molecule for pharmaceutical use.

A similar process for the preparation of crystalline losartan potassium is disclosed in the patent WO 02094816 where, unlike the said process, an aqueous solution of potassium hydroxide is not used but solid potassium hydroxide is added to an alcoholic solution of losartan.

According to the process of the synthesis disclosed in US Pat. No. 5,130,439 and US Pat. No. 5,310,928, crystalline losartan potassium is formed *via* substituted boric salts with hydrolysis of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole with sulfuric acid in tetrahydrofuran and subsequent rinsing on the column with dipotassium hydrogen phosphate and by concentrating the rinsed aqueous solution with added *i*-propanol. This patent describes the process for the preparation of losartan potassium by spray drying.

From the disclosure it is clear that potassium hydroxide and dipotassium hydrogen phosphate are commonly used as the base in conversion of losartan to losartan potassium. Generally, under nonaqueous conditions, certain salts may be also prepared with alkali or alkali-earth alcoholates which is already known with certain

heterocyclic compounds according to European Patent Application 495626 but not with losartan itself.

It has been found that losartan potassium exists in two polymorphic forms [Pharm. Res. 10 (1993), 900]. The authors of US Pat. No. 5,608,075 present that polymorphic form I characterized by DSC endotherm at 229.5°C while heating transforms to polymorphic form II characterized by the endothermic peak of melting at 273.2°C.

From the disclosure of US Pat. No. 5,859,258 it is clear that a polymorphic form itself does not provide the needed suitable physicochemical properties. It has been found that uncontrolled crystallization may lead to formation of large three-dimensional complexes which are unsuitable for incorporation into a pharmaceutical formulation and, in the said patent, a strictly controlled process is disclosed wherein, surprisingly, 14 different requirements should be met to obtain a suitable form of the particles for pharmaceutical use. The need for such strictly controlled process due to non-ruggedness may result in a number of errors in large-scale production which may essentially influence the final product.

Crystal forms are identified by the physicochemical methods to measure the parameters dependent on the molecular environment. The most useful methods are: differential thermal analysis, infrared spectroscopy, solid-state nuclear magnetic resonance and X-ray diffraction.

Infrared spectroscopy is a method which on the basis of absorption of the IR light detects low-energy transitions particularly at a level of the bonds resulting from molecular vibrations and oscillations. They predominantly depend on the nature of the molecules and its bonds, and may be also influenced by the molecule environment. Therefore, it has become a widely accepted method for characterization of polymorphs. It is not always necessary that different crystal forms are also expressed on different IR spectra. Distinctions may be manifested in the presence or absence of defined oscillations or vibrations, in strengthened or

weakened bands and in shifts of the wavelengths in individual oscillations or vibrations.

Solid-state ^{13}C nuclear magnetic resonance is a useful method for structural elucidation of solid samples. This way, individual polymorphic modifications can be determined. In a simple way, solvates may be characterized, and conformational polymorphs may also be examined in a very simple way. The spectra with high resolutions and the signals with good intensities are obtained by the CP/MAS (cross-polarization / magic angle spinning spectrum) scanning technique. [Sedon K.R. et al, Crystal Engineering: The Design and Application of Functional Solids, Kluwer Academic Publishers, 1999]. It would be expected that two identical spectra are obtained when two different polymers are recorded since in both cases two carbons are bonded in the same way. In fact, a distinction is evident because equivalent compounds are in different chemical environments [Bugay D.E.: Magnetic Resonance Spectrometry in: Brittain H.G., Physical Characterization of Pharmaceutical Solids]. Characterization of the structure of the samples which are pure and comprise only one crystal form is the most simple. If there is a mixture of different forms, chemical shifts are obtained which may mutually overlap thus being misleading in characterization of a crystal structure. This may lead to an erroneous conclusion there is a new polymorphic modification.

Essentially, the crystal lattice may be characterized more precisely by X-ray diffraction than by infrared spectroscopy and NMR methods for solid samples wherein the changes are detected only on those atoms and bonds which directly interfere with the neighbouring molecules. From the X-ray diffraction pattern of a good orderly state of a large crystal a spatial assignment pattern of the molecule can be precisely defined, and by recording powder samples, the distinctions between different crystal lattices may be characterized but the position of individual atoms cannot be exactly characterized. In addition to identification of a different assignment of the molecules in a crystal, indicating a different crystal form, information about the orderly state level or crystallinity can be obtained from the powder diffractogram wherein less orderly state is exhibited in broadening of the bands in the diffractogram. Extremely disordered state of a solid substance is

an amorphous state which does not exhibit a repetitive pattern of molecular orientation in a solid substance therefore resulting in a diffuse scattering of X-ray light which is expressed by continuous diffraction in the diffractogram over the entire scanned region. Using the described method, several different crystal forms in the substance can be revealed and their mass ratio characterized. X-ray powder diffraction is a method useful in distinguishing different crystal forms and for distinguishing an amorphous form and polymorphic forms.

It is known that because of administration into the body, pharmaceutical active substances are required to be especially pure substances in order to prevent occurrence of undesirable toxic effects. The substances are purified by a variety of methods such as for the solid substances, among others, thermally induced recrystallization, precipitation with solvents or reagents, extractions and washings, pH regulation, chromatographic methods. The applicants of EP 2533310 purified the finished product by recrystallization of an amphoteric substance from acetonitrile. Subsequent patents such as WO 9310106 and WO 9517396 disclose more complicated and longer processes for affording losartan potassium of high purity which comprise thermally induced crystallization of the amphoteric substance and potassium salt, use of column chromatography and use of adsorptive carriers. The applicants of the patent EP 1106611 and US Pat. No. 6,350,880 report that these methods are unsatisfactory and propose purification *via* the salt of losartan with monobasic acids such as chlorides, bromides and *p*-toluenesulfonates. In the final phase, however, it is a single step recrystallization from the acid salt to the alkaline salt with potassium hydroxide resulting in the formation of larger amounts of potassium salt of the anionic moiety of losartan which can be coprecipitated on losartan potassium as impurity, the crystallization itself is carried out in acetonitrile which is not a recommended solvent for the last step because of toxicity.

EP 324377 describes the pharmaceutical compositions wherein 1 to 500 mg of losartan daily is combined with other substances, for example diuretics, and sets forth hypertension as the indication. WO 9219228 discloses optimized compositions of tablets suitable for direct compression.

Description of the figures

Figure 1: DSC curve of a potassium salt of losartan identified as form I

Figure 2: DSC curve of a sodium salt of losartan isolated in a crystalline form

Figure 3: DSC curve of a magnesium salt of losartan

Figure 4: DSC curve of a calcium salt of losartan

Figure 5: IR spectrum of a potassium salt losartan identified as form I

Figure 6: a section of the IR spectrum shown in Figure 5

Figure 7: IR spectrum a sodium salt of losartan isolated in a crystalline form

Figure 8: a section of the IR spectrum shown in Figure 7

Figure 10: IR spectrum of a calcium salt losartan

Figure 11: ^{13}C CP/MAS NMR spectrum of the sample of a sodium salt of losartan identified as form I

Figure 12: X-ray powder diffractogram of a potassium salt of losartan identified as form I

Figure 13: X-ray powder diffractogram of a sodium salt of losartan isolated in a crystalline form

Figure 14: X-ray powder diffractogram of a sodium salt of losartan prepared in an amorphous form

Figure 15: X-ray powder diffractogram of a magnesium salt of losartan

Figure 16: X-ray powder diffractogram of a calcium salt of losartan

Description of the invention

The present invention discloses purification of losartan with conversion of amphoteric substance – salt thereof – amphoteric substance.

For the preparation of the quality salts of losartan for pharmaceutical use highly pure amphoteric losartan is demanded. In preparing quality losartan and losartan potassium, respectively, of high purity for the preparation of finished pharmaceutical compositions, it has been surprisingly found that effective

purification is obtained by conversion *per se* of amphoteric substance – alkali salt – amphoteric substance with no need for additional purification of these intermediates by crystallization. The processes *via* the concrete salts provide various degrees of purification, the most effective processes are *via* sodium and potassium salts which are formed as crystalline salts from the solvents.

The object of the present invention is to provide a purification process of losartan and the preparation of the salts useful in said purification process, and in respect to the known prior art, has an essential advantage because losartan potassium purified *via* these two salts has shown to be purer than losartan potassium prepared according to the disclosure in WO 9310106 and which does not reach the pharmaceutical quality, and no procedure for additional purification of the product is reported in said reference. As evident from the examples, the purification *via* both a sodium salt and a potassium salt appears to be an effective method since highly pure amphoteric losartan has been obtained from which more pure losartan potassium is prepared than in the prior art described procedure. Surprisingly, the process *via* a sodium salt affords better ruggedness as the influence of pH change on a yield is essentially smaller than in case of preparation of a potassium salt, and a yield *per se* is also better in preparing a sodium salt than in preparing a potassium salt as shown in Table 1.

Purification	*via* Na salt		*via* K salt		*via* Ca salt	
Step	Purity	Yield	Purity	Yield	Purity	Yield
Starting losartan	98.44%		98.44%		98.4%	
Salt	99.42%	82%	99.67%	77%	98.16%	91.9%
Losartan	99.74%	94%	99.29%	93%	98.98%	91.0%
Losartan K	99.91%	94%	99.88%	96%	99.81%	88.9%

Table 1: Comparison of the yields and purities of losartan purified *via* different salts

This conversion of the substances affords effective purification and the obtained amphoteric losartan has a low level of impurities and is suitable for the preparation of a potassium salt for pharmaceutical use, from such amphoteric

losartan also the other high-quality alkali and alkali-earth salts of losartan may be prepared.

According to the present invention, crude losartan was first purified by the following process: losartan dissolved in alcohol was converted to a potassium or a sodium salt of losartan, the resulting salt was isolated in a crystal form, the resulting isolated salt was dissolved in water or a mixture of water and an organic solvent, an inorganic acid to pH between about 3.6 and about 3.8 was added to the resulting solution, the resulting solution was cooled below about 10°C whereupon losartan precipitated or crystallized and this way obtained losartan was further washed with an organic solvent.

From losartan purified in this manner, losartan potassium was prepared by the procedures known in the art; for example, by the addition of potassium hydroxide solution. In an analogous way, other alkali and alkali-earth salts of losartan may be prepared having essentially less impurities than if prepared from amphoteric losartan isolated directly from the reaction. Such salts are suitable for pharmaceutical use.

The purification process of losartan using conversion of amphoteric substance – alkali salt or alkali-earth salt – amphoteric substance involves two subprocesses, that is, preparation of the salt and its isolation, and further preparation of amphoteric losartan from said salt.

Preparation of alkali or alkali-earth salt of losartan and its isolation:

We have found that according to the first part of the process, alkali or alkali-earth salts of losartan may be prepared if losartan is dissolved in a convenient solvent, for example, in alcohol or a mixtures of alcohol and an aprotic solvent, preferably in *i*-propanol to obtain a concentration of losartan about 170 g/l and at a temperature between about 38°C and about 40°C, an aqueous solution of alkali or alkali-earth metal hydroxide is added to pH between about 9 and about 12.5,

preferably to pH about 10 during over 15 min to about 1 hour, preferably over half an hour, whereupon it is distilled until all azeotropic mixtures are removed.

The procedure for preparation of the alkali-earth salts of losartan was more thoroughly studied and they were prepared by adding nonaqueous alkali-earth metal alcoholate or alkali-earth metal hydroxide to the solution losartan in a suitable solvent or a mixture of solvents, for example in *i*-propanol, prepared to obtain a concentration of about 170 g/l, and the reaction mixture was stirred at elevated temperature between about 40°C and about 85°C, preferably at the reflux temperature.

In all examples the alkali or alkali-earth salts of losartan from the *i*-propanol solution prepared this way were precipitated with a nonpolar solvent, preferably with *n*-heptane at a low temperature, preferably at a temperature below about 10°C and were isolated according to the standard procedures. Crystalline potassium and sodium salts and surprisingly amorphous magnesium and calcium salts result from said preparation. A crystalline potassium salt is in the art known form of losartan, and we have characterized it as crystalline form I but no sodium salt has been characterized yet. Surprisingly, the crystals of losartan sodium appear to be larger and more nicely shaped if a mixture of solvents in which they are formed contains some water. The salts of losartan, according to the present invention, may be also prepared in the form with the bound water, which can be influenced by a choice of the conditions, for example pH. Crystalline losartan sodium prepared at pH of about pH 12 retains between about 3.5% and about 4.5% water even after drying and releases water only at a temperature about 100°C.

The preparation of a magnesium salt with magnesium alcoholate, for example with magnesium ethoxide is preferable since the use of magnesium hydroxide because of poor solubility and prevalent conversion to insoluble magnesium oxide is most impractical. Surprisingly, we have found that better results in respect to the yield and quality are also obtained by using sodium or potassium alcoholates in nonaqueous media, for example in alcohol, instead of using aqueous solutions

of sodium or potassium hydroxide, and the process itself is also less time-consuming since it does not require expel of water with azeotropic distillation. The easiest way to obtain the solution of sodium or potassium alcoholate itself is by dissolving commercially available sodium or potassium *t*-butoxide, or by adding metal sodium to alcohol, however, said solution should be prepared just prior to addition of losartan whereas potassium *t*-butoxide may be added directly to the solution of losartan in alcohol. Yield when using a known method with hydroxide is sensitive to pH and presence of water, in said method an impact of these two factors is almost nullified, being particularly evident in the preparation of a potassium salt.

The most convenient process for the preparation of losartan potassium is as follows: losartan is dissolved in a suitable solvent, for example alcohol, preferably *i*-propanol, to obtain a concentration of about 370 g/l and after adding potassium *t*-butoxide, a potassium salt of losartan is separated with the addition of a nonpolar solvent, for example carbon hydride, preferably *n*-heptane, and a yield of separation of the salt from the solution is additionally increased. Losartan potassium is isolated by simple filtration and drying. By this method, analogously a sodium salt of losartan is also prepared using sodium *t*-butoxide in that conversion.

Preparation of losartan from alkali-earth or alkali salts thereof

According to the purification process of losartan with conversion of amphoteric losartan – alkali salt or alkali-earth salt – amphoteic losartan, further a selected salt, prepared according to one of the described procedures, was dissolved in about 5- to about 20-fold amount of water, preferably to obtain a concentration of about 100 g/l, at a temperature of about 5°C to about 25°C, preferably in a temperature range from 21°C to 25°C, an organic solvent was added, preferably ethyl acetate, and acidified with and inorganic acid, preferably with a concentrated inorganic acid, still more preferably with sulfuric (VI) acid to pH between about 3.6 and about 3.8, preferably to pH about 3.7, thereafter the reaction mixture was

cooled to a temperature of about 0°C to about 15°C, preferably below 10°C and losartan was isolated according to the standard procedures.

We have found that from the above described processes for the preparation of the salts of losartan, a magnesium salt and a calcium salt are amorphous as characterized by the X-ray powder analysis. On the other hand, this way isolated potassium salt is crystalline form I which is known in the prior art and we have found that thus far unknown sodium salt is also crystalline, and if its aqueous solution is lyophilized amorphous losartan sodium is obtained, as well.

Further, pharmaceutical compositions comprising new highly pure alkali or earth-alkali salts and pharmaceutically acceptable excipients are also the object of the present invention. The pharmaceutical composition can be in a dosage form suitable for oral or parenteral administration, and is indicated, for example, for the treatment of hypertension, thus, the pharmaceutical composition, the object of said invention, can be, for example, in the form of tablets, capsules, pellets, granules and suppositories.

Solid pharmaceutical dosage forms can be coated, for example, to improve pelletability or to adjust disintegration and absorption, respectively.

In concordance with the object of the present invention, we have prepared film coated tablets by the method of the direct dry blend or by the dry granulation method. Pharmaceutically usable alkali or alkali-earth salts of losartan, purified according to the disclosed process, for example, are mixed with acceptable excipients, for example: lactose, microcrystalline cellulose, starch and aerosil, magnesium stearate and compressed into tablets.

Experimental part

The prepared amorphous form of potassium salt of losartan was described and characterized with the following physicochemical methods by comparing the determined properties with in literature available data that is with the

characteristics of the crystalline salt of losartan prepared according to US Pat. No. 5,608,075 or as described in the examples:

1. Melting point determination
2. Differential thermal calorimetry
3. NMR spectroscopy
4. IR spectroscopy
5. X-ray powder diffraction.

A crystalline potassium salt, prepared according to the processes from the present invention *via* the process of conversion of amphoteric losartan – potassium salt – amphoteric losartan was recognized as Form I, and was identical to that prepared according to US Pat. No. 5,608,075.

Sodium, magnesium and calcium salts, thus far unknown in the prior art, were also characterized by the above physicochemical methods. We have found that losartan sodium, prepared according to the above processes and described in detail in the examples, exists in a crystalline form and an amorphous form, losartan calcium and losartan magnesium are identified only in an amorphous form

1. Melting point

The melting point was determined by the method of visual inspection on a microscope with a heated table, and by Thiele method.

In crystalline losartan potassium a change is visible at about 230°C, it is the temperature known from the literature as a conversion region to Form II.

A difference between the melting points of crystalline and amorphous losartan sodium is distinct. A crystalline form has a melting point 191–196°C, an and amorphous form 171–177°C.

Melting of calcium and magnesium salts was not observed below 300°C.

2. Differential thermal analysis

A differential dynamic calorimeter Perkin Elmer Pyris 1 DSC was used.

Losartan potassium has the first endothermic change above 230°C which would agree with the temperature of conversion of Form I to Form II, known from the literature. Above said temperature considerably sample decomposition and changes are highly visible.

Crystalline losartan sodium has a melting point according to DSC method at 195°C which is concordant to the measurement on Kofler microscope. However, a greater endothermic change may be already observed in the region about 110°C, which is thought to result from the loss of crystal water. Amorphous losartan sodium does not exhibit these changes, conversions above 240°C are characterized by decomposition of the samples. Already above 150°C a very stretched conversion is barely visible, on Kofler microscope observed as a melting-like visible change between 170 and 180°C.

DSC thermograms of the samples of losartan sodium and losartan magnesium are similar to the thermograms of amorphous losartan sodium at temperatures above 200°C, only decomposition of the samples is observed in the approximately same temperature region with somewhat different dynamics of thermal fluxes.

DSC thermograms are shown in Figures 1 to 4.

3. ^{13}C CP/MAS NMR spectroscopy of the solid substance

A Varian NMR spectrometer Unity plus 300 for recording of the samples by the ^{13}C-NMR Solid-State CP-MAS method. The samples were measured with TOSS at spinning 10 kHz, pulse (90) 4.4 μs (tpwm=3600).

A crystalline form of potassium salt exhibits sharp peaks as shown Figure 11, a record of all chemical shifts is in Table 2:

Chemical shift (ppm)
14.1
17.1
21.0
27.8
30.4
/
50.0 (wide)
123.8
126.5
130.3
131.7
134.6
136.1
141.7
146.6
148.1
163.0

Table 2: Chemical shifts of the solid-state sample of losartan potassium recorded by the NMR method CPMAS

4. IR (infrared) spectroscopy

An infrared spectrometer »Bio-Rad FTS-60, Digilab-Division« was used.
The recorded IR spectra are illustrated in Figures 5 to 10, the most distinct absorption peaks are between 1510 and 700 cm^{-1} and are also shown in the table below, while the values for form II of crystal salt are taken from the literature [Pharm. Res. 10 (1993), 900]:

Crystalline losartan potassium form I)	Crystalline losartan potassium (form II)	Crystalline losartan sodium	Amorphous losartan sodium	Losartan magnesium	Losartan calcium
1507		1507	1507	1507	1508
1497		1498	1494	1495	1494
1472		1474	/	/	/
1460		1461	1460	1461	1461
1423		1426	1425	1426	1426
1406		1408	1408	1409	1409
1378		weak	1380	1380	1380
1358	1357	1360	1358	1359	1358
1342	/	1342	/	/	/

1260		1264	1256	1258	1258
/		1140	1144	1150	1148
1133		1132	merged	merged	merged
1113		1109	1108	1108	1108
1074		1080	1074	1075	1075
/		1011	1013	1014	1014
1008		1008	1006	1006	1006
996		/	/	/	/
954	/	958	954	953	954
/		949	/	/	/
934	940	937	933	934	934
886	/	/	weak	weak	878
844		/	/	/	/
841		839	/	/	/
826		820	824	824	824
789		785	787	787	786
763	754	753	761	760	760
merged with 763		740	743	merged with 760	743
713	/	weak	weak	714	714

Table 3: Characteristic bands [cm^{-1}] in the IR spectra of different salts of losartan in the region between 1550 and 700 cm^{-1}

The IR spectrum of crystalline losartan sodium is more similar to form I of crystalline losartan potassium than amorphous losartan sodium, however it is evidently distinct from a potassium salt by the absence of the peaks at the intervals of the wave-numbers 995–1000 and 870–890 cm^{-1} and changes in the region between 820 and 850 cm^{-1}, identified by the presence of the peaks 839±1 and 820±1 cm^{-1}. Amorphous losartan sodium distinguishes from crystalline losartan sodium by the absence of the peaks in the regions of the wave-numbers 1472 ± 5, 1342 ± 5 and between 835 and 845 cm^{-1}.

All amorphous forms of losartan salts, both potassium, sodium, magnesium or calcium, have the equivalent IR spectrum, differences are within an error of analytical and software perception of the wave-number value of the band peak and differ from the other crystalline salts by the absence of the absorption bands in the regions of the wave-numbers 1472 ± 5, 1342 ± 5 and between 835 and 845 cm^{-1}. This may be explained that there are no specific bands in the spectrum which would result from the influence of cations on the energy states of bonding, and

the other bands are a result of interior molecular events because intermolecular influences due to an unorderly amorphous state are dispersed and thus undistinguishable in an IR spectrum.

5. X-ray powder analysis

The samples were recorded on an apparatus Philips PW1710 using the reflexion technique under the conditions: CuKα radiation, range from 2° to 37° 2θ with a 0.04y 2θ step, integration time 1 second.

The X-ray powder diffractogram of losartan potassium, shown in Figure 12, indicates characteristic bands at the angles which in the prior art are characteristic for polymorph form I.

In amorphous losartan sodium, the X-ray powder diffractograms of losartan sodium indicate the absence of diffractions and indisputable amorphous structure of the material contrary to the crystalline sample which shows sharp peaks which indicate high crystallinity. Both diffractograms are shown in Figures 13 and 14.

The X-ray powder diffractograms of losartan magnesium and losartan calcium indicate an evident amorphous structure of the samples irrespective of the mode of their preparation. The diffractograms of the typical samples of magnesium and calcium salts are shown Figures 15 and 16.

In the following examples which further illustrate but in no way limit the present invention, the best modes of the preparation of novel pharmaceutically useful forms of losartan including new methods of purification and isolation according to the present invention are presented.

Example 1

Losartan crude (2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl] methyl]-1H-imidazole)

A blend of 129.80 g of 5-[2-(4'-bromomethylbiphenylyl)]-2-triphenylmethyl-2H-tetrazole, 43.4 g of 2-*n*-buthyl-4-chloro-5-hydroxymethyl-1H-imidazole and 38.27 g of potassium carbonate in 550 ml of N,N-dimethylacetamide was mixed at a temperature of 0–5°C for 8 hours and at room temperature overnight. To the mixture 8.02 g of $NaBH_4$ and 18 ml of water was added, cooled to room temperature and stirred for 3 hours. The reaction mixture while stirring vigorously was poured into 1.1 l of water and filtered, the precipitate was washed with 550 ml of water, dried *in vacuo* at room temperature over silica gel.

2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(triphenylmethyl-2H-tetrazol-5-yl) [1,1'biphenyl-4-yl] methyl]imidazole was obtained which was recrystallized from chlorobutane and ethyl acetate to yield 66.77 g after the final reaction and purification after drying.

To a solution of 67.77 g of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(triphenylmethyl-2H-tetrazol-5-yl)[1,1'biphenyl-4-yl]methyl]imidazole in 316 ml of tetrahydrofuran (THF) while stirring 105.9 g of 12% HCl was added at a temperature of 23°C over one hour. The mixture was stirred at room temperature overnight. 30% of NaOH was added a temperature to 22°C over one hour until the pH of 12.5 (ca. 100 ml) was attained. THF was evaporated at a temperature of 60°C and demineralized water was added to the original volume. The precipitate formed was filtered, washed with 2 x 50 ml of demineralized water and discarded. The water phase was extracted with 1 x 50 ml of toluene. The organic layer was separated and 124 ml of ethyl acetate was added to the water phase. The reaction mixture while stirring vigorously was acidified with concentrated H_2SO_4 at a temperature 21–25°C to pH 3.6–3.8, cooled below 10°C and stirred for 1 hour. The produced precipitate was filtered, washed with 130 ml of ethyl acetate, filtered again and dried *in vacuo* at a temperature of 50°C overnight to yield 40.8 g of losartan in an amphoterous form.

Example 2

Formation of a sodium salt of losartan – method 1

To 40.81 g of losartan from Example 1 in 235 ml of *i*-propanol was added the solution of 5.5 g of sodium hydroxide in 5.7 ml of water at a temperature 38–40°C to pH 12 over half an hour. Approximately 35 ml of the azeotropic mixture *i*-propanol / water was removed by distillation. 140 ml of *n*-heptane was added and stirred at room temperature until a white precipitate was formed. The resulting precipitate was diluted with 55 ml of *n*-heptane, filtered, washed with 110 ml of *n*-heptane and dried *in vacuo* at 50°C to yield 35.0 g of a sodium salt of losartan.

Melting point: 191–196°C

Water according to Karl-Fisher: 4.2%.

Assay of sodium 4.4% (5.0% calculated to the dry matter)

Example 3

Formation of a sodium salt of losartan – method 2

To 40.81 g of losartan from Example 1 in 235 ml of *i*-propanol was added the solution of 5.5 g of sodium hydroxide in 5.7 ml of water at a temperature 38–40°C to pH 12 over half an hour. Approximately 35 ml of the azeotropic mixture *i*-propanol / water was removed by distillation. 140 ml of *n*-heptane was added and stirred at room temperature until a white precipitate was formed. The resulting precipitate was diluted with 55 ml of *n*-heptane, filtered, washed with 110 ml of *n*-heptane and dried *in vacuo* at 50°C to yield 37.0 g of a sodium salt of losartan.

Melting point: 190–198°C

Water according to Karl-Fisher: 0.3%.

Example 4

Formation of a sodium salt of losartan – method 3

To 40.81 g of losartan from Example 1 in 120 ml of *i*-propanol was added 9.28 g of sodium *t*-butoxide. The reaction mixture clarified. 145 ml of *n*-heptane was

added and stirred at room temperature until a white precipitate was formed. The resulting precipitate was filtered and washed with 165 ml n-heptane, dried at 40°C *in vacuo* to yield 37.0 g of a sodium salt of losartan.

Melting point: 191–196°C

Assay of sodium 4.7% (5.2% calculated to the dry matter).

Example 5

Formation of a potassium salt of losartan – method 1

To 40.81 g of losartan from Example 1 in 235 ml of *i*-propanol was added the solution of 5.5 g of potassium hydroxide in 5.7 ml of water at a temperature 38–40°C to pH 12 over half an hour. Approximately 35 ml of the azeotropic mixture *i*-propanol / water was removed by distillation. 141.5 ml of *n*-heptane was added and stirred at room temperature until a white precipitate was formed. The resulting precipitate was diluted with 54 ml of *n*-heptane, filtered, washed with 108 ml of *n*-heptane and dried *in vacuo* at 50°C to yield 21.36 g of losartan potassium.

Example 6

Formation of a potassium salt of losartan – method 2

To 10.2 g of losartan from Example 1 in 59 ml of *i*-propanol was added the solution of 1.4 g of potassium hydroxide in 1.5 ml of water a temperature 38–40°C to pH 10 over half an hour. Approximately 19 ml of the azeotropic mixture *i*-propanol / water was removed by distillation. 36 ml of *n*-heptane was added and stirred at room temperature until a white precipitate was formed. The resulting precipitate was diluted with 14 ml of *n*-heptane, filtered, washed with 26 ml of *n*-heptane and dried *in vacuo* at 50°C to yield 8.57 g of losartan potassium.

Example 7

Formation of a potassium salt of losartan – method 3

To 40.81 g of losartan from Example 1 in 110 ml of *i*-propanol was added 10.86 g of potassium *t*-butoxide a temperature between 10°C and 25°C. The reaction mixture was clarified whereupon a dense white precipitate was formed. 150 ml of *n*-heptane was added and stirred at room temperature for 1 hour. It was filtered and washed with 75 ml of *n*-heptane, dried at 50°C C *in vacuo* overnight to yield 43.25 g of losartan potassium.

Example 8

Formation of a magnesium salt of losartan

To 40.81 g of losartan from Example 1 in 235 ml of *i*-propanol was added 6.07 g of magnesium ethoxide and stirred at the reflux temperature overnight. It was hot filtered, 650 ml of *n*-heptane was added and cooled to room temperature to precipitate the product. It was filtered and washed with 110 ml of *n*-heptane, and dried *in vacuo* at 50°C to yield 37.9 g of losartan magnesium.
Melting point: above 300°C
Assay of magnesium 2.9% (3.2% calculated to the dry matter).

Example 9

Formation of a calcium salt of losartan

To 40.81 g of losartan from Example 1 in 235 ml of *i*-propanol was added 3.92 g of calcium hydroxide and stirred at the reflux temperature for 1 hour, and hot filtered. 410 ml of *n*-heptane was added to the filtrate and cooled to room temperature. The solvent was decanted from a resinous residue and 820 ml of *n*-heptane was added. It was stirred until a white precipitate was crystallized which was filtered, washed with 110 ml of *n*-heptane and dried *in vacuo* at 50°C to yield 39.2 g of losartan calcium.
Melting point: above 300°C

Assay of calcium 4.0% (4.7% calculated to the dry matter).

Example 10

Losartan purified – method 1

35 g of a sodium salt of losartan was dissolved in 350 ml of water, 106 ml of ethyl acetate was added and acidified at a temperature 21 to 25°C to pH 3.6–3.8 with concentrated sulfuric acid, cooled below 10°C and stirred for 1 hour. The formed precipitate was filtered, washed with 120 ml of ethyl acetate, filtered again and dried *in vacuo* at 50°C over night to yield 29.3 g of losartan.

Example 11

Losartan purified – method 2

42.66 g of a potassium salt of losartan was dissolved in 430 ml of water, 130 ml of ethyl acetate was added and acidified at a temperature 21 to 25°C to pH 3.6–3.8 with concentrated sulfuric acid, cooled below 10°C and stirred for 1 hour. The formed precipitate was filtered, washed with 145 ml of ethyl acetate, filtered again and dried *in vacuo* at 50°C over night to yield 36.6 g of losartan.

Example 12

Losartan purified – method 3

37.9 g of a magnesium salt of losartan was dissolved in 388 ml of demineralized water, 120 ml of ethyl acetate was added and acidified at a temperature 21 to 25°C to pH 3.6–3.8 with concentrated sulfuric acid, cooled below 10°C and stirred for 1 hour. The formed precipitate was filtered, washed with 130 ml of ethyl acetate, filtered again and dried *in vacuo* at 50°C over night to yield 32.3 g of losartan.

Example 13

Losartan purified – method 4

38.0 g of a calcium salt of losartan was dissolved in 380 ml of water, 115 ml of ethyl acetate was added and acidified at a temperature 21 to 25°C to pH 3.6–3.8 with concentrated sulfuric acid, cooled below 10°C and stirred for 1 hour. The formed precipitate was filtered, washed with 130 ml of ethyl acetate, filtered again and dried *in vacuo* at 50°C over night to yield 36.2 g of losartan.

Example 14

Preparation of pharmaceutically usable losartan potassium *via* crystalline losartan sodium

To 20.4 g of crude losartan (chromatographic purity 98.73%) in 120 ml of *i*-propanol was added the solution of 2.75 g of sodium hydroxide in 2.9 ml of water at a temperature 38–40°C to pH 10 over half an hour. Approximately 18 ml of the azeotropic mixture *i*-propanol / water was removed by distillation. 70 ml of *n*-heptane was added and stirred at room temperature until a white precipitate was formed. The resulting precipitate was diluted with 28 ml of *n*-heptane, filtered, washed with 55 ml of *n*-heptane and dried *in vacuo* at 50°C to yield 18.5 g of a crystalline sodium salt of losartan (yield: 87%, chromatographic purity: 99.42%).

The substance obtained was dissolved in 185 ml of water, 56 ml of ethyl acetate was added and acidified at a temperature 21–25°C to pH 3.6–3.8 with concentrated sulfuric acids, cooled below 10°C and stirred for 1 hour. The formed precipitate was filtered, washed with 64 ml of ethyl acetate, filtered again and dried *in vacuo* at a temperature 50°C overnight to yield 16.5 g of losartan (yield of the phase: 94%, chromatographic purity: 99.74%).

The resulting product was dissolved in 45 ml of *i*-propanol, 4.39 g of potassium *t*-butoxide between 10°C and 25°C was added. The reaction mixture clarified whereupon a dense, white precipitate was formed. 60 ml of *n*-heptane was added and stirred at room temperature for 1 hour. It was filtered and washed with 30 ml of *n*-heptane, dried *in vacuo* at 50°C overnight to yield 16.9 g of losartan potassium (yield of the phase: 94%, chromatographic purity: 99.91%, overall yield: 77%).

Example 15

Preparation of pharmaceutically usable losartan potassium *via* crystalline losartan potassium

As already described in Example 4, to 10.2 g of crude losartan from Example 1 (chromatographic purity 98.73%) in 59 ml of *i*-propanol was added to the solution of 1.4 g of potassium hydroxide in 1.5 ml of water at a temperature 38–40°C to pH 10 over half an hour. Approximately 19 ml of the azeotropic mixture *i*-propanol / water was removed by distillation. 36 ml of *n*-heptane was added and stirred at room temperature until a white precipitate was formed. The resulting precipitate was diluted with 14 ml of *n*-heptane, filtered, washed with 26 ml of *n*-heptane and dried *in vacuo* at 50°C to yield 8.57 g of losartan potassium (yield: 77%, chromatographic purity: 99.67%).

The resulting potassium salt of losartan was dissolved in 86 ml of water, 26 ml of ethyl acetate was added and acidified at a temperature 21–25°C to pH 3.6–3.8 with concentrated sulfuric acids, cooled below 10°C and stirred for 1 hour. The formed precipitate was filtered, washed with 29 ml of ethyl acetate, filtered again and dried *in vacuo* at 50°C overnight to yield 7.35 g of losartan (yield of the phase: 93%, chromatographic purity: 99.82%).

The resulting product was dissolved in 20 ml of *i*-propanol, 1.96 g of potassium *t*-butoxide in a temperature range between 10°C and 25°C was added. The reaction mixture clarified whereupon a dense, white precipitate was formed. 27 ml of *n*-

heptane was added and stirred at room temperature for 1 hour, filtered and washed with 13 ml of *n*-heptane, dried *in vacuo* at 50°C overnight to yield 7.66 g of losartan potassium (yield of the phase: 96%, chromatographic purity: 99.88%, overall yield: 69%).

Example 16

Comparative example of the preparation of a potassium salt according to known prior art

To 40.81 g of losartan (chromatographic purity 98.73%) in 153 ml of *i*-propanol was added the mixture of 10 g of potassium hydroxide, 5.1 ml of water and 100 ml of *i*-propanol at a temperature 38–40°C to pH 10–11 over half an hour. Approximately 140 ml of the solvent (*i*-propanol / water mixture) was removed by distillation and 92 ml of *n*-heptane was added. It was stirred at room temperature until a white precipitate was formed. It was diluted with 54 ml of *n*-heptane, filtered, washed with 70 ml of *n*-heptane and dried *in vacuo* at 50°C to yield 38.4 g of losartan potassium (yield: 86%, chromatographic purity: 99.67%).

Claims

1. A sodium salt of losartan.

2. The sodium salt of losartan according to claim 1 characterized in that it is in a crystal form and has its X-ray powder diffractogram diffractions at 2θ = 6,2°, 14,5°, 18,2°, 18,8°, 21,6°, 23,5°, 24,8° and 25.5°.

3. The sodium salt of losartan according to claim 1 characterized in that it exists in a crystal form and has a melting point between 190 and 200°C.

4. The sodium salt of losartan according to claim 1 characterized in that it exists in a crystal form with the bound water wherein an amount of water is between about 3.5% and about 4.5%, and a loss of the bound water on drying between about 100 and about 120°C.

5. Alkali-earth metal salts of losartan.

6. The alkali-earth metal salt of losartan according to claim 5 selected between a magnesium salt or a calcium salt.

7. The process for the preparation of alkali-earth or alkali salts of losartan characterized in that it comprises the following steps:
   a) addition of an alkali or alkali-earth metal alcoholate to the solution of losartan in alcohol or a in a mixture of alcohol and an aprotic solvent;
   b) precipitation or crystallization of the resulting salt;
   c) isolation of the resulting precipitated or crystallized salt by filtration and centrifuging.

8. The process according to claim 7 wherein an alkali-earth salt is selected between a magnesium salt or a calcium salt; an alkali salt is selected between a potassium salt or a sodium salt.

9. The process according to claims 7 and/or 8 characterized in that an alkali metal alcoholate is selected between sodium or potassium *t*-butoxide.

10. The process according to any of claims 7 to 9 characterized in that the alcohol used is *i*-propanol.

11. The process according to any of claims 7 to 10 characterized in that the alkali or alkali-earth salt is precipitated or crystallized by adding an aprotic solvent.

12. The process for the preparation of a sodium salt of losartan characterized in that it comprises the following step:
    a) addition of a sodium hydroxide solution to the solution of losartan to pH between about 9 and about 12;
    b) precipitation or crystallization of the resulting salt by adding an aprotic solvent;
    c) isolation of the resulting precipitated or crystallized salt by filtration and centrifuging.

13. The process according to any of claims 7 to 12 characterized in that an aprotic solvent is *n*-heptane.

14. The process of purification characterized in that it comprises the following steps: conversion of losartan to the salt; further isolation of that salt; conversion of the isolated salt to losartan.

15. The process of purification of losartan characterized in that it comprises the following steps:
    a) preparation of the alkali or alkali-earth salt of losartan according to any of claims 7 to 11, or preparation of the sodium salt of losartan according to claims 12 and/or 13;
    b) preparation of losartan from the resulting isolated salt by acidifying with an inorganic acid in an organic solvent.

16. The process according to claim 15 characterized in that an alkali salt of losartan is selected between a potassium salt or a sodium salt and the said salt of losartan is isolated in a crystal form; and, the preparation of losartan from said isolated salt by acidifying with an inorganic acid in an organic solvent characterized in that it comprises the following steps:

a) dissolving of the isolated salt in water or in a mixture of water and an organic solvent;
b) addition of an inorganic acid to the resulting solution to pH between about 3.6 and about 3.8;
c) cooling of the resulting solution below about 0°C whereupon losartan is precipitated;
d) washing further of the resulting precipitated losartan with an organic solvent.

17. The process according to claims 15 and/or 6 characterized in that an inorganic acid is sulfuric (VI) acid.

18. The process according to claims 15 and/or 16 characterized in that an organic acid is ethyl acetate.

19. The use of an alkali or alkali-earth salt of losartan in the purification process according to claims 14 and/or 15.

20. The use of a crystalline sodium salt of losartan in the purification process of losartan according to any of claims 14 to 18.

21. The pharmaceutical composition which comprises crystalline sodium salt of losartan as the active substance and pharmaceutically acceptable excipients.

22. The pharmaceutical composition which comprises an alkali-earth salt of losartan as the active substance and pharmaceutically acceptable excipients.

23. The use of a crystalline sodium salt of losartan for the preparation of the medicament.

24. The use of a crystalline losartan sodium salt according to claim 23 for the preparation of a medicament for the treatment of hypertension.

Lek Pharmaceuticals d.d.

Abstract

A process of purification of 2-*n*-butil-4-kloro-5-hidroksimetil-1-[[2'-(1H-tetrazol-5-il)[1,1'-bifenil]-4-il]metil]-1H-imidazole by transition amphoter - alkali and earth alkali salts – amphoter , which proceeds via novel isolated alkali and earth alkali salts of losartan.

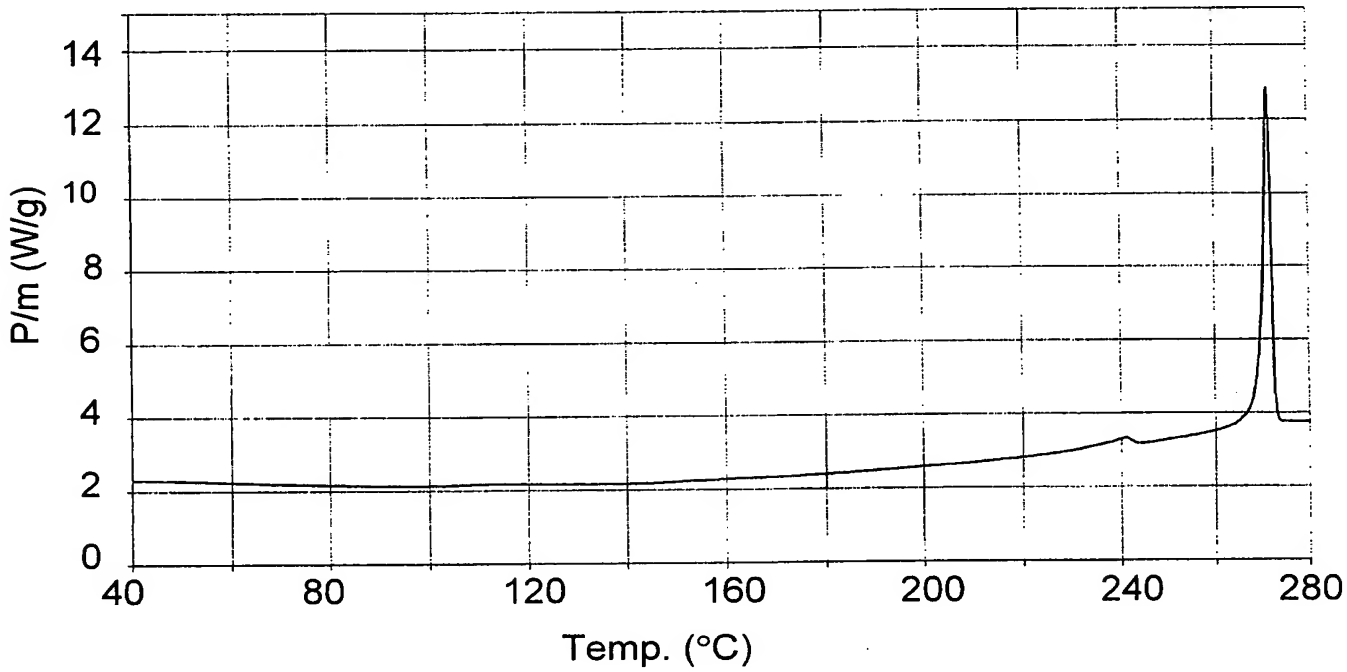


Figure 1

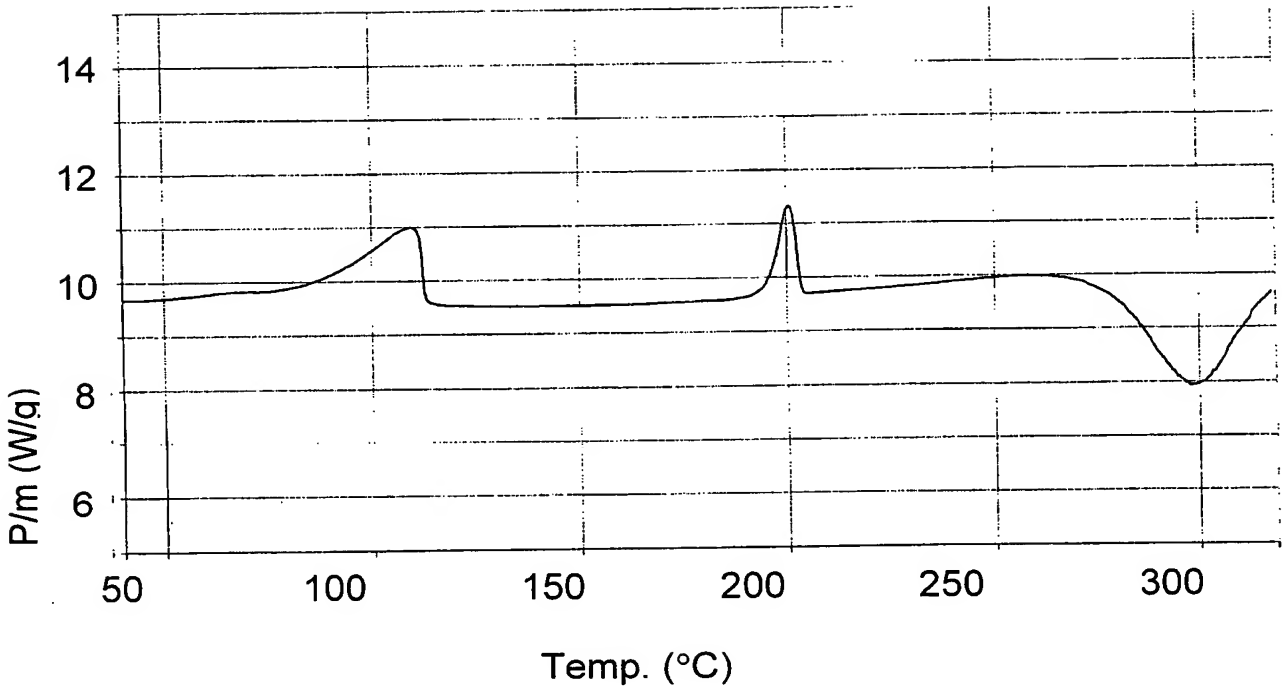


Figure 2

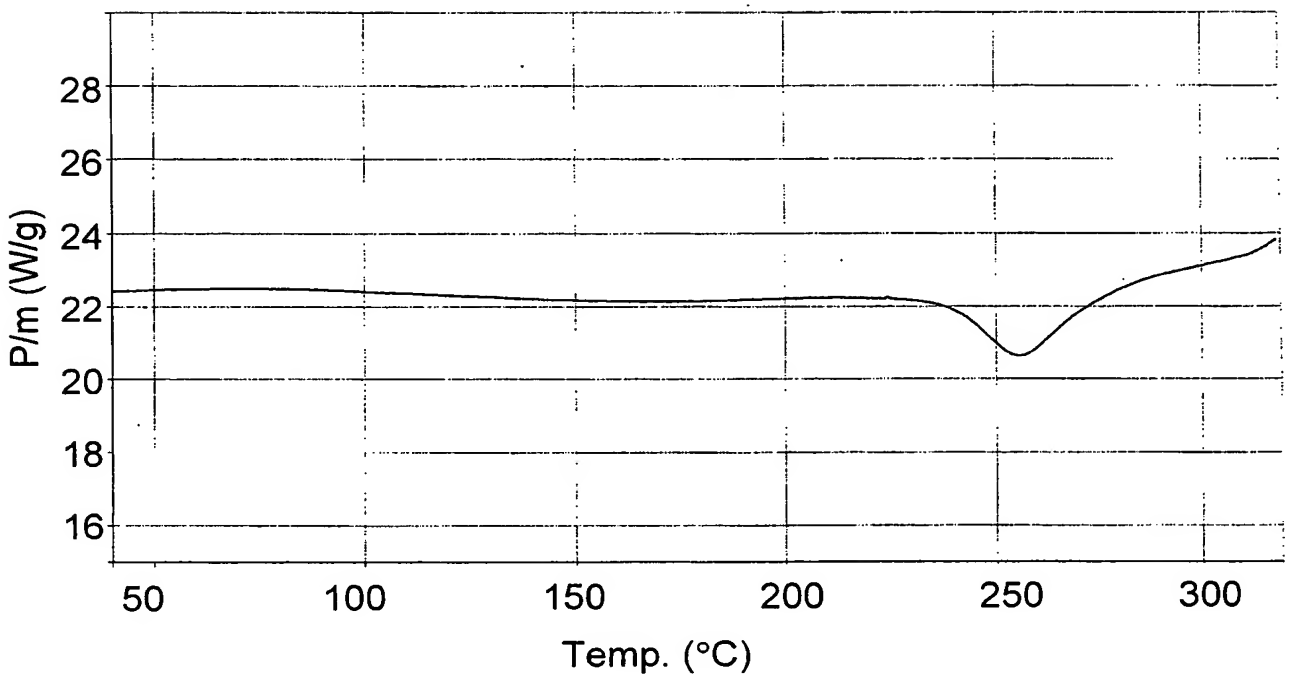


Figure 3

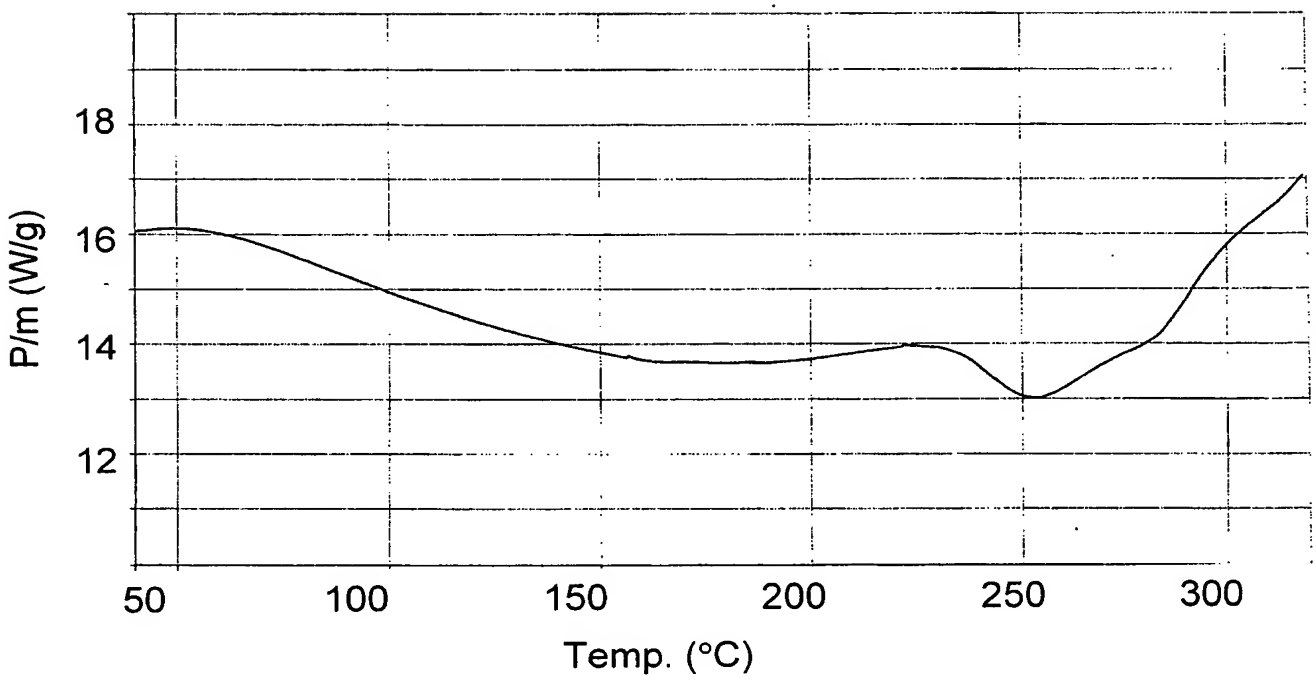
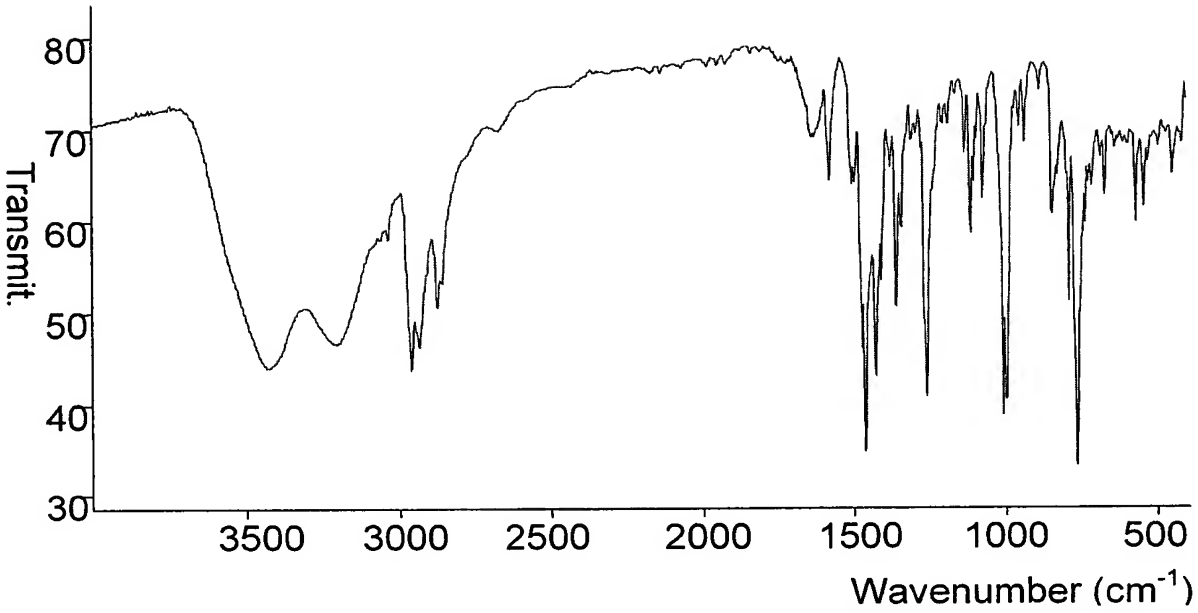


Figure 4



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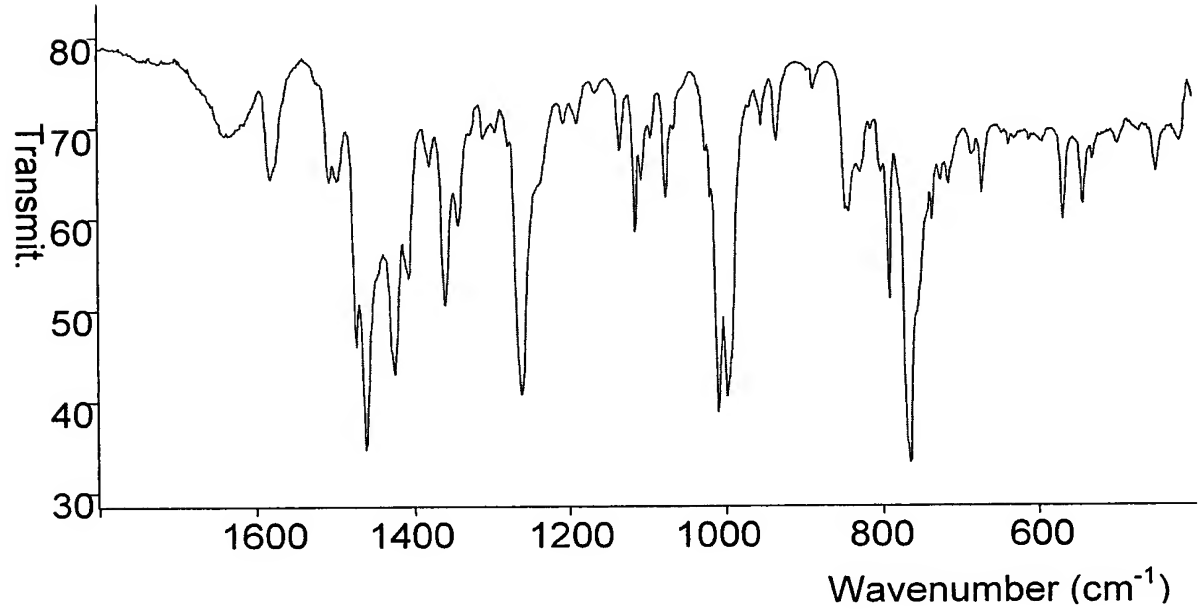

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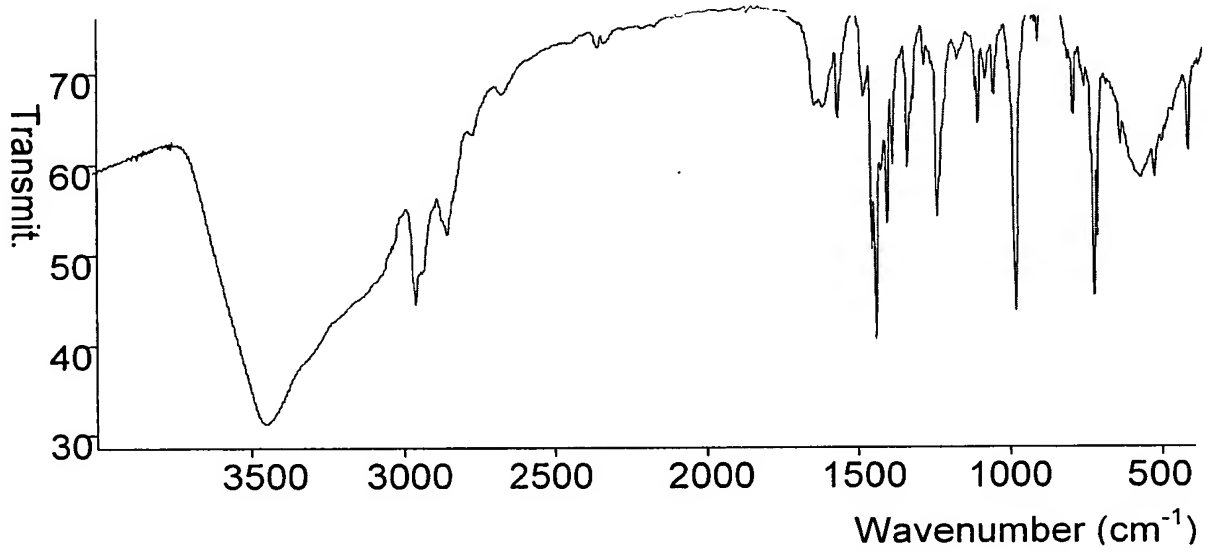

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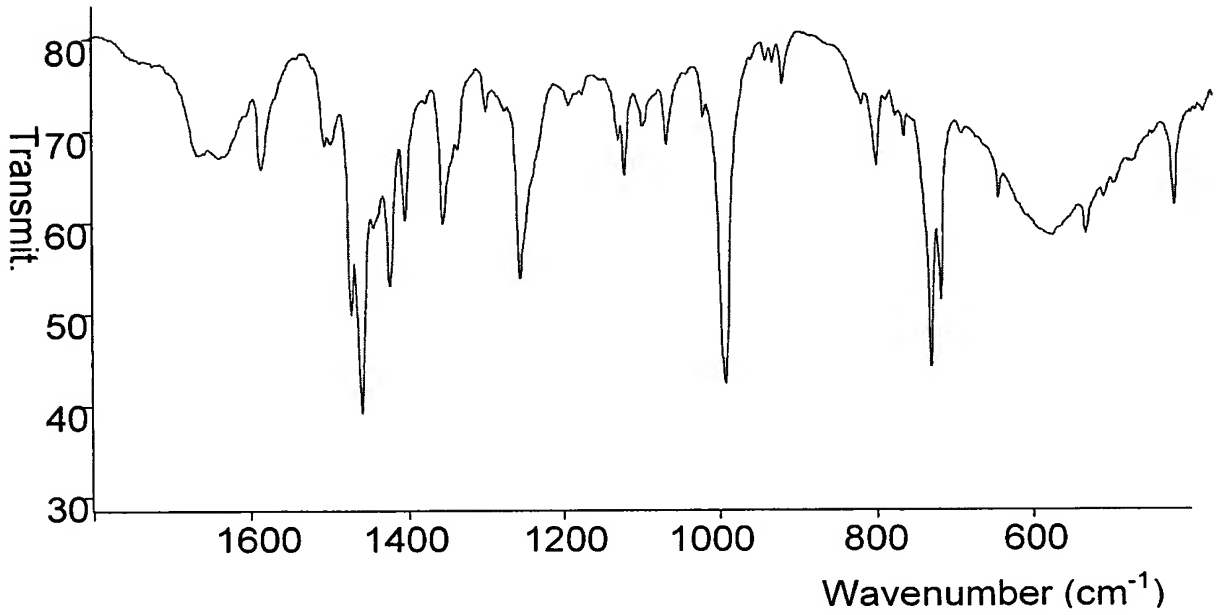
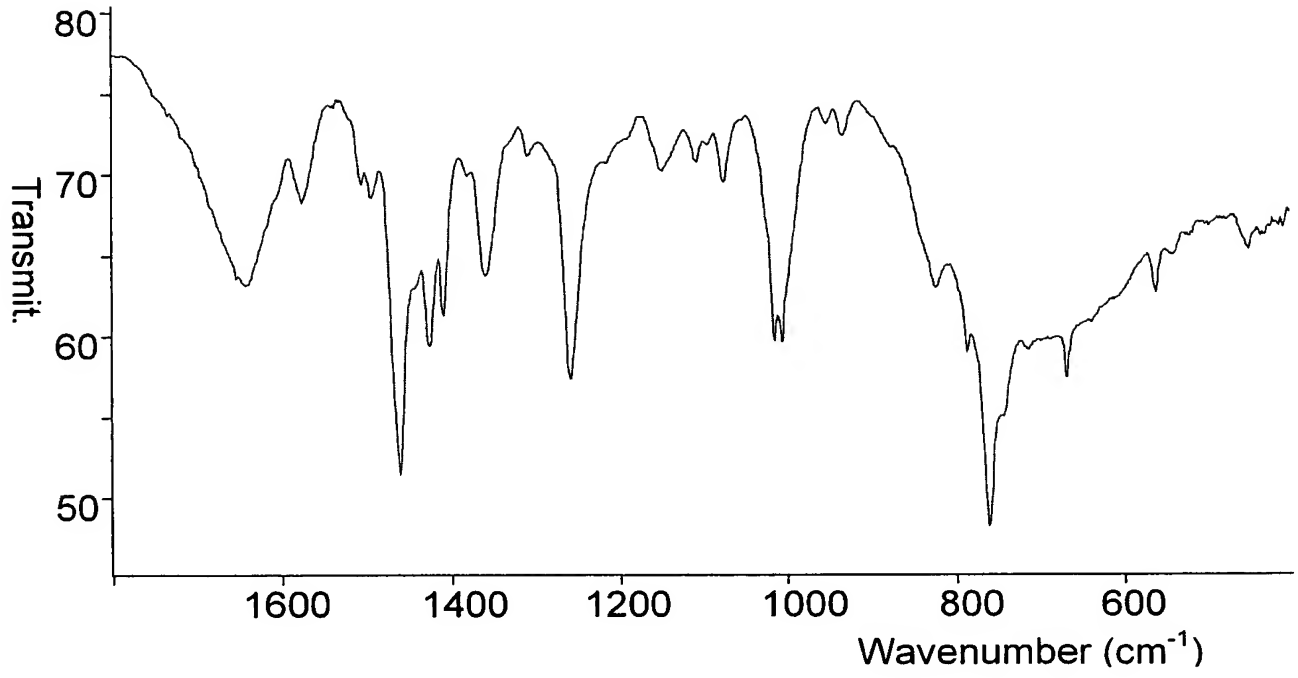


Figure 8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Wavenumber (cm-1)

Figure 9

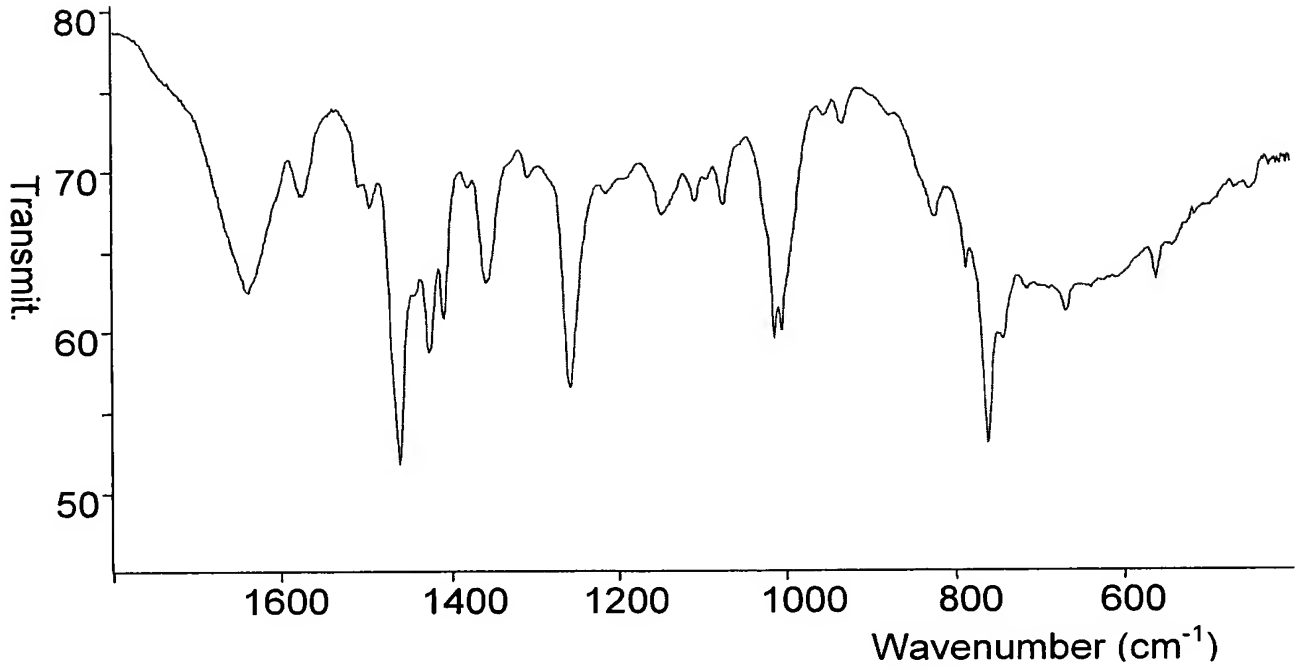
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Figure 10

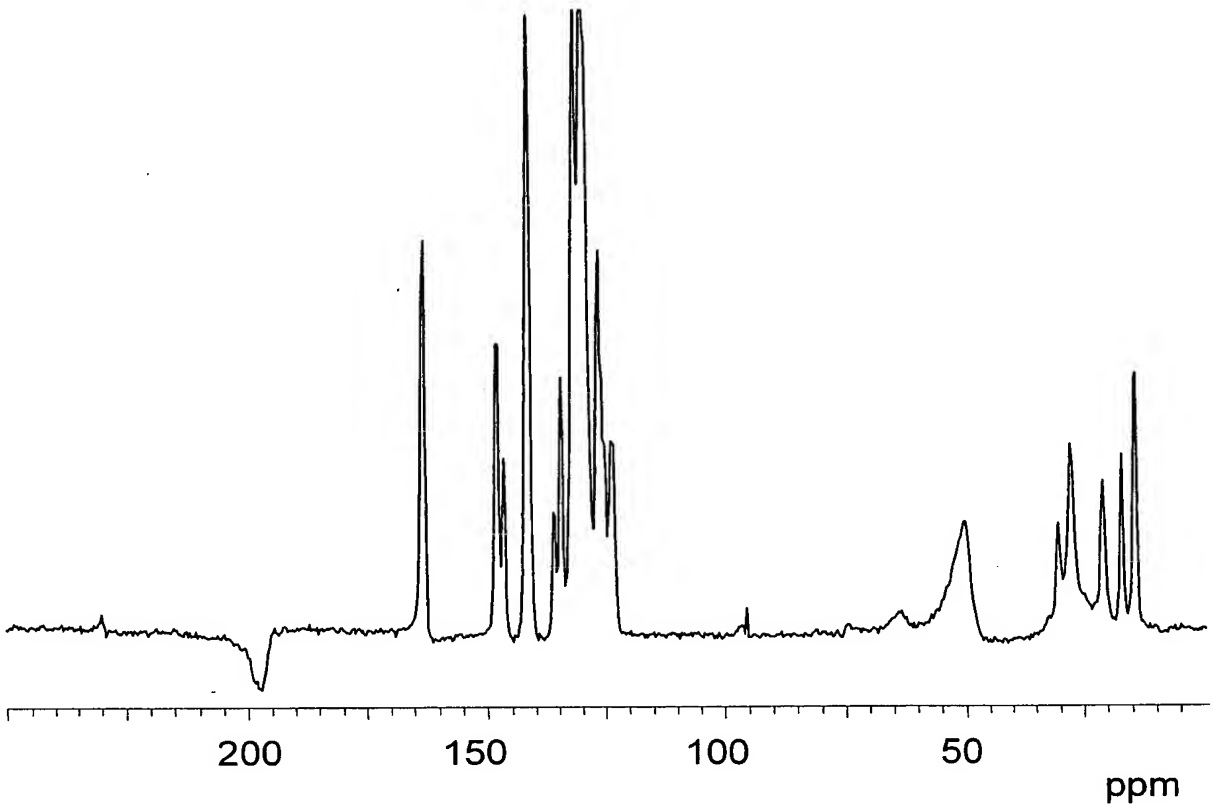


Figure 11

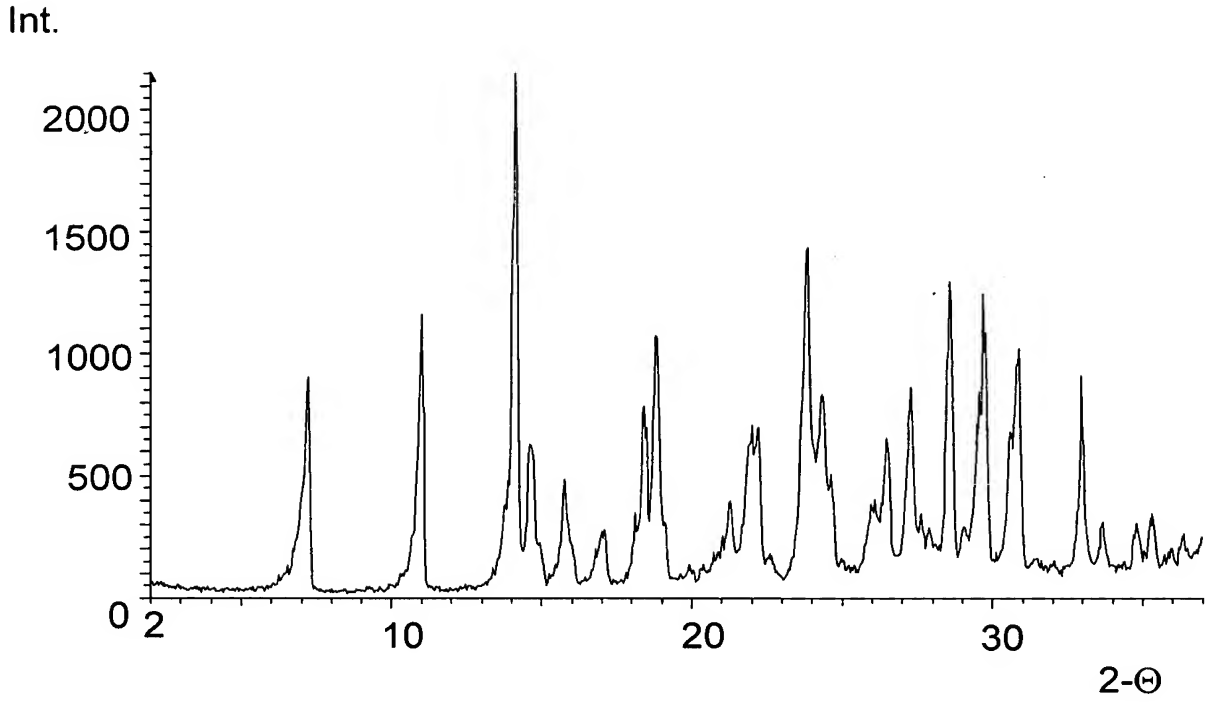
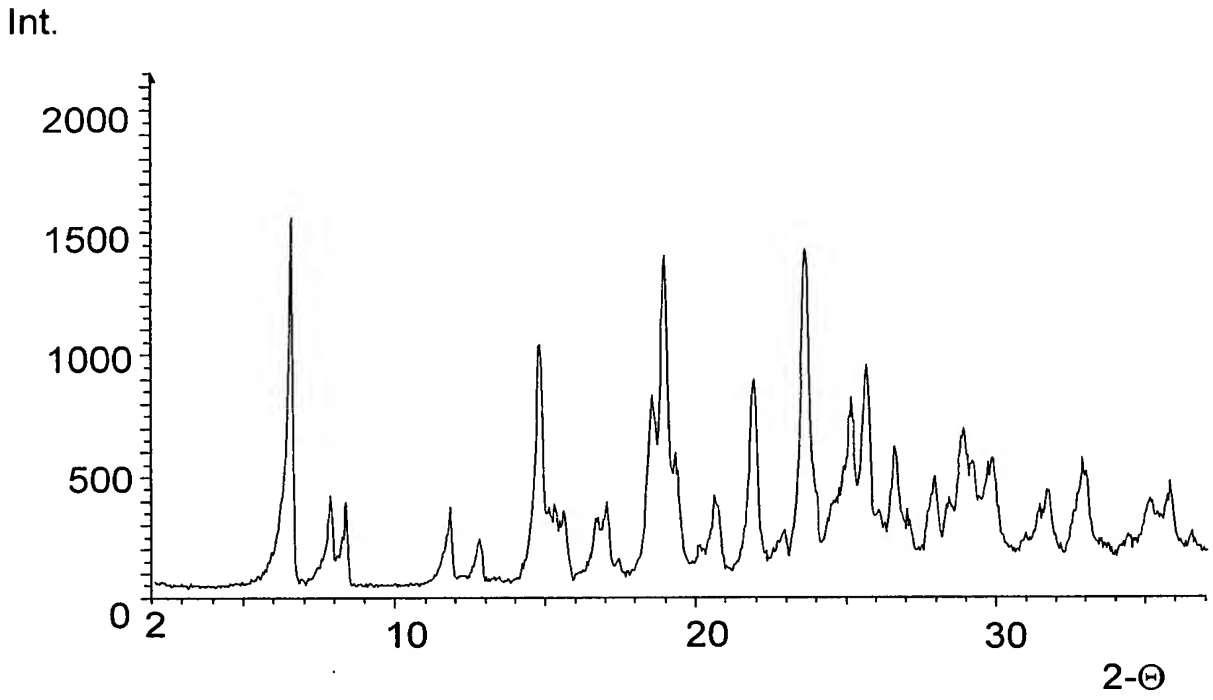


Figure 12



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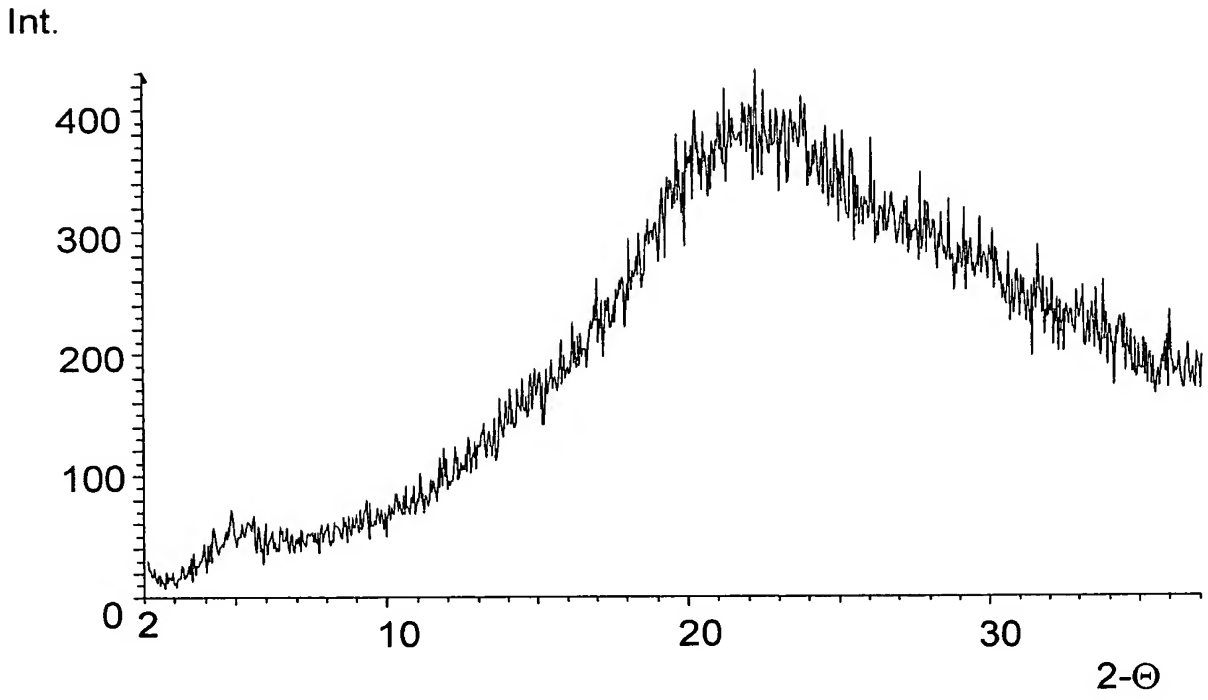

Figure 14

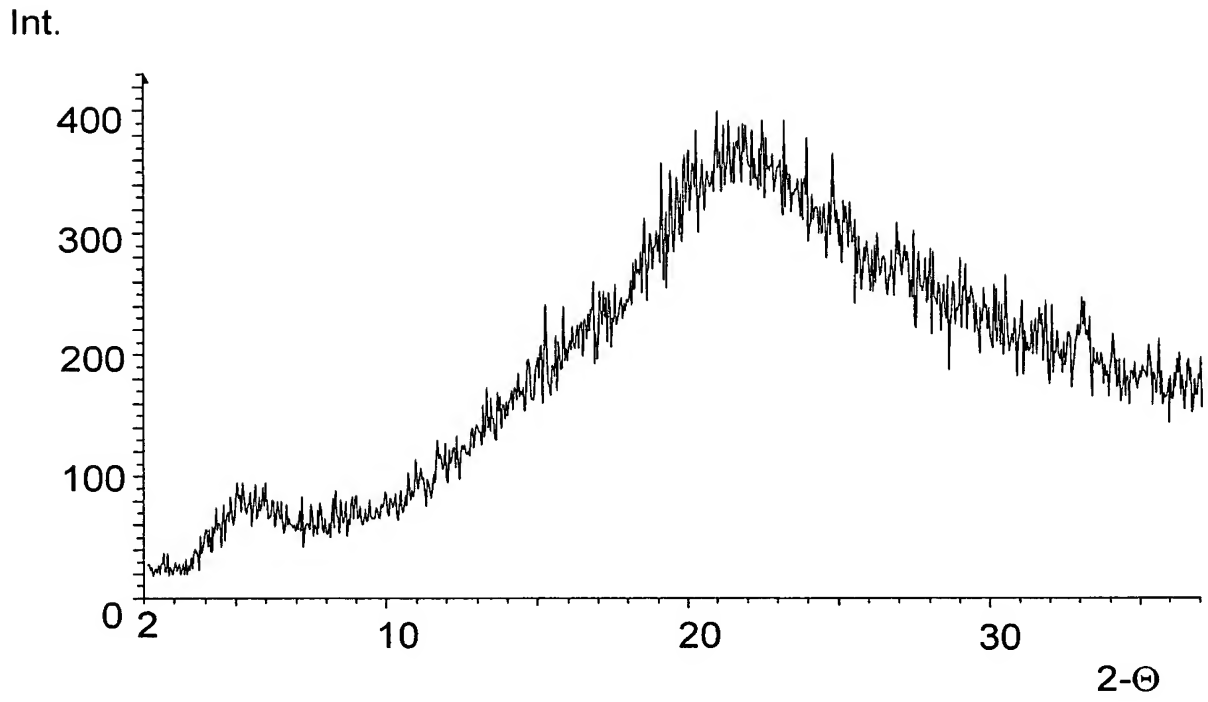

Figure 15

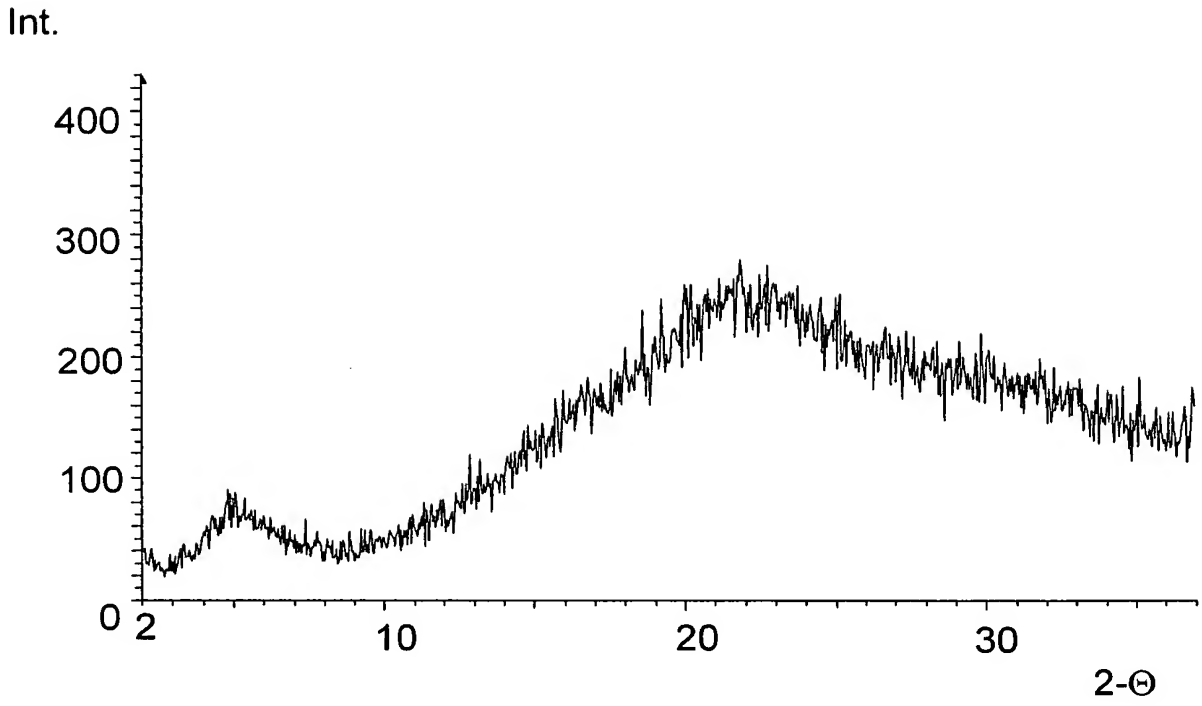

Figure 16

The undersigned Djurdjica Mandrino, permanent court interpreter for the English language, appointed by Decree No. 756-4/91, issued on 11th of February 1991 by the Ministry of Justice and Administration, Republic of Slovenia, hereby declares that this document entirely corresponds to the original Slovene text.

Ljubljana, 8 June 2005